REMARKS

Claims 51-78 are pending.

Claims 64-78 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention/species.

Amendments

Specification

The Related Applications section at paragraph [1] has been amended to replace the attorney docket number "05882.0178.PZUS03" for the prior provisional application filed September 30, 2003, with its USPTO application number, "60/508,149."

The description for Figure 2 at paragraph [34] has been amended with the phrase "from Figure 1" to clarify that the sequence identifiers in Figure 1 correspond to the sequences in Figure 2.

The SEQ ID NOs. in paragraph [35] at page 8 have been corrected to accurately identify the sequences depicted in Figure 3.

The term "http://" has been deleted from the specification thereby eliminating all embedded hyperlinks.

Drawing

Replacement drawing for Figure 3 is submitted herewith. The drawing includes corrected labels for the amino acid sequences depicted from SEQ ID NOS: 1 and 7, to SEQ ID NOs: 46 and 47, respectively. These labels correctly correspond to the SEQ ID NOs in the substitute sequence listing submitted herewith.

Substitute Sequence Listing

Applicants submit herewith a paper copy and computer readable form of a substitute sequence listing in accordance with 37 CFR § 1.825(a) and (b).

This substitute sequence listing corrects minor errors discovered in Applicants' previous substitute sequence listing submitted on July 10, 2006. The substitute sequence listing of SEQ ID NO: 20 includes amino acids 137-143 which are shown in Figure 5 of the application as

originally filed, but were inadvertently omitted from the first submitted sequence listing. Additionally, the substitute sequence listing includes SEQ ID NOs: 46 and 47. These two amino acid sequences were depicted in Figure 3A and 3B of the application as filed but were inadvertently mislabeled as corresponding to SEQ ID NOS:1 and 7.

The substitute sequence listing contains no new matter.

Applicants specifically request that the Examiner enter the sequence listing into the file for the application.

Claims

Minor amendments have been made to Claims 51, 55-59 in view of the restriction/election of sequences, and to further clarify the subject matter of the invention.

Applicants submit that the above amendments add no new matter to the application.

Response

Objections to Specification

The disclosure has been objected to as including embedded hyperlinks. As stated above, the term "http://" has been deleted from the specification thereby eliminating all embedded hyperlinks.

The disclosure has been objected to because the Brief Description of the Drawings for Figure 2 lists "SEQ ID NOs:1-12" but Figure 2 itself does not include these SEQ ID numbers. Applicants note however that Figure 2 does use the same sequence identifiers as used in Figure 1 (*e.g.*, V_H 1.0, V_L 1.0, etc.), and Figure 1 clearly labels each of these common sequence identifiers with SEQ ID NOs: 1-12. To further clarify this correspondence between the sequences in Figure 1 and Figure 2, Applicants have amended the Brief Description for Figure 2 to refer to Figure 1.

Accordingly, Applicants believe that all objections to the specification have been overcome.

Claim Rejections - 35 USC § 112, Second Paragraph

Claim 51 has been rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite insufficient antecedent basis for the recitation of "the constant region" in line 8. Applicants have amended claim 51 so as to recite expressly "a constant region." This rejection is therefore obviated and this rejection should be withdrawn.

Claims 51 and 55 have been rejected that as allegedly vague and indefinite as to whether both a heavy chain variable region and a light chain variable region are required. The Examiner appears to suggest that the use of a semicolon between the heavy chain and light chain clauses in the claim renders this ambiguous. Applicants respectfully disagree, and submit that this use of semicolons is clear and a conventional claims drafting element. Applicants point out that the recitation of the conjunctive term "and" after the light chain clause clearly indicates that the claimed antibodies are required to include all three recited structural features: (1) a heavy chain variable region; (2) a light chain variable region; and (3) a constant region. Accordingly, claims 51 and 55 are definite, and the rejection should be withdrawn.

Claim Rejections - 35 USC § 112, First Paragraph – Written Description

Claims 51-58, and 63, are rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. The written description rejection appears to be based on a perceived lack of disclosure of representative species to support a claimed genus. Specifically, the Examiner has stated that "Applicants need to provide examples of sequences that are 95% identical which still retain binding capabilities to alpha5beta1 integrin;" and "identification of any particular portion of the structure that must be conserved." Applicants respectfully disagree with this rejection, and as described below, can identify disclosure in the present application that specifically address the Examiner's ground for rejection.

Applicants point out that SEQ ID NOs: 1 and 7 represent the heavy chain variable (V_H) and light chain variable region (V_L) sequences of the mouse anti-α5β1 antibody, IIA1. The specification however, not only disclose the IIA1 V_H and V_L sequences, which have 100% identity, but also disclose five other distinct humanized versions of the IIA1 V_H and V_L (SEQ ID NOs: 2-6 and 8-12). *See e.g.,* Figures 1 and 2. As shown in Figure 2, each of these is a different sequence variant of SEQ ID NOs: 1 or 7 with less than 100% identity. For example, as shown in Figure 2 V_H1.0 (SEQ ID NO: 2) includes substitutions at 17 amino acids of the total of 124 positions relative to SEQ ID NO: 1. The specification also discloses the heavy and light chain sequences of HuM200 (SEQ ID NOs: 31 and 32), which represent an additional humanized anti-α5β1 antibody, and therefore another variant on SEQ ID NOs:1 and 7. *See e.g.,* Figure 13 and paragraph [198] at page 55.

Although sharing less than 100% structural identity, each of the antibodies represented sequences has the functional ability to specifically recognize α5β1 integrin. *See e.g.,* paragraph [69] at page 14; paragraph [125] at page 32; paragraph [199] at page 55; and Figure 26. Thus, the present specification discloses a range of structural variants that all share the common functional characteristic of specifically binding α5β1.

It should also be noted that each of the variant sequences disclosed in the present specification is in effect supported by the other variants. For example, written support for variants of HuM200 (SEQ ID NOs: 31 and 32) with less than 100% sequence identity may be found in SEQ ID NOs: 1-6 and 7-12, respectively.

With regard to the Examiner's allegation that the specification fails to identify any portion of the sequence structure that must be conserved, Applicants respond that Figure 2 clearly shows the particular amino acid positions and types of amino acid variations that may be tolerated by IIA1. *See also,* description at paragraph [96] at page 23.

In conclusion, as described above, the present specification provides a range of representative α5β1 antibodies that share common structural and functional characteristics and therefore demonstrates that the Applicants were fully in possession of the subject matter of claims 51-58 and 63 and the application fully complies with the written description requirement of § 112 ¶ 1.

Applicants believe they have fully answered the Examiner's grounds for the written description rejection and respectfully request that the rejection should be withdrawn.

Claim Rejections - 35 USC § 112, First Paragraph – Enablement

Claims 51-63 are rejected under 35 U.S.C. §112, first paragraph for lack of an enabling disclosure. Specifically, the Examiner has alleged that the specification does not reasonably provide enablement for chimeric or humanized antibodies that have heavy and light chains with at least 95% sequence identity to SEQ ID NOs: 1, 16, 20, 25, 28, and 31, as well as 7, 18, 22, 26, and 32, respectively. Applicants respectfully disagree with the rejection and provide the following remarks responding to the Examiner's reasons for it.

As a preliminary matter, Applicants wish to point out that claims 59-63 do not recite the "at least 95% sequence identity" limitation, therefore the Examiner does not appear to have presented *prima facie* grounds for rejecting these claims as not enabled. Indeed, the Examiner

concedes that the specification is enabling for HuM200-G4 and HuM200-g2m3 (corresponding to SEQ ID NOs. 31 and 32), therefore at least claim 62 should be fully enabled. The Examiner provides no reason why claims directed to antibodies with specifically recited sequences are not enabled.

With respect to Claims 51-58, which do recite the "at least 95% sequence identity" limitation, Applicants believe that the Examiner's application of the Wands factors is flawed because several examples from the application were not considered. The Examiner appears to have based his analysis on the incorrect assumption that the instant specification contains examples of only two humanized or chimeric antibodies: HuM200-G4 and HuM200g2m3. The Examiner does not appear to have considered the five additional humanized antibodies whose heavy and light chain variable region sequences are disclosed as SEQ ID NOs:2-6 and 8-12. *See e.g.,* paragraphs [33] and [34] and Figures 1 and 2. As described in the remarks above related to written description, the specification teaches that these humanized antibodies include variant sequences have less than 100% sequence identity (*e.g.,* SEQ ID NO: 2 has approximately 87% sequence identity to SEQ ID NO:1). The specification also teaches that these humanized antibodies specifically recognize α5β1 and can be purified using a pH-sensitive purification procedure. *See e.g.,* paragraph [69] at page 14, and paragraph [125]. Thus, the present specification provide substantial direction to one of ordinary skill in the art by exemplifying a range of structurally variant antibody sequences spanning the scope of claims 51-58.

The Examiner also suggests that the claims are overbroad for encompassing antibodies that include amino acid substitutions and variations in the complementary determining regions (CDRs). Although the CDR sequences are conserved in the specific examples of humanized anti-α5β1 integrin heavy and light chain sequences shown in Figure 2, the present specification provides the necessary teachings to allow one of ordinary skill to prepare, screen, and purify a broad range of a chimeric or humanized anti-α5β1 integrin antibodies beyond those having sequences specifically exemplified in the disclosure. *See e.g.,* paragraphs [102]-[135] and various references cited therein. Applicants wish to point out that the pending claims are all directed to a chimeric or humanized anti-α5β1 integrin antibody. While Applicants acknowledge that there is an extremely large number of theoretical sequences that will <u>not</u> specifically recognize α5β1 integrin, these sequences should not be relevant to the Examiner's enablement analysis. The Examiner has not presented any reason why one of skill could not use the

teachings of the present disclosure without undue experimentation to isolate chimeric or humanized antibodies that specifically recognize anti-α5β1 integrin yet also include some variation in the CDR (*e.g.*, a single amino acid change) or other regions. Consequently, the pending claims should not be considered overbroad.

In view of the foregoing, Applicants believe they have fully answered the Examiner's grounds for the enablement rejection and respectfully request that the rejection should be withdrawn.

Claim Rejections - Double Patenting

Claims 51, and 54-63, are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as allegedly unpatentable over claims 1-8 of copending Application No. 10/830,956. Similarly, claims 51, and 54-63, also are provisionally rejected as directed to an invention not patentably distinct from claims 1-8 of commonly assigned 10/830,956. As shown in the PAIR system, a response to restriction submitted in July 10, 2006 in 10/830,956 withdrew claims 1-8 from consideration. Therefore Applicants believe that the instant double patenting rejection is rendered moot and should be withdrawn.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants believe all claims now pending in this application are in condition for allowance.

If the Examiner believes a telephone conference would expedite prosecution of this application, please call the undersigned at (650) 798-3524.

Respectfully submitted,

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